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**PARP-1 deficiency increases the severity of disease in a mouse model of multiple sclerosis.**

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**Public Summary:**

**Scientific Abstract:**

Poly(ADP-ribose) polymerase-1 (PARP-1) has been implicated in the pathogenesis of several central nervous system (CNS) disorders. However, the role of PARP-1 in autoimmune CNS injury remains poorly understood. Therefore, we studied experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis in mice with a targeted deletion of PARP-1. We identified inherent physiological abnormalities in the circulating and splenic immune composition between PARP-1(-/-) and wild type (WT) mice. Upon EAE induction, PARP-1(-/-) mice had an earlier onset and developed a more severe EAE compared with WT cohorts. Splenic response was significantly higher in PARP-1(-/-) mice largely because of B cell expansion. Although formation of Th1 and Th17 effector T lymphocytes was unaffected, PARP-1(-/-) mice had significantly earlier CD4<sup>+</sup> T lymphocyte and macrophage infiltration into the CNS during EAE. However, we did not detect significant differences in cytokine profiles between PARP-1(-/-) and WT spinal cords at the peak of EAE. Expression analysis of different PARP isozymes in EAE spinal cords showed that PARP-1 was down-regulated in WT mice and that PARP-3 but not PARP-2 was dramatically up-regulated in both PARP-1(-/-) and WT mice, suggesting that these PARP isozymes could have distinct roles in different CNS pathologies. Together, our results indicate that PARP-1 plays an important role in regulating the physiological immune composition and in immune modulation during EAE; our finding identifies a new aspect of immune regulation by PARPs in autoimmune CNS pathology.

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